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LETTER TO THE EDITORS

The era of the new directly acting antivirals: Has the time come for kidney transplant only in compensated cirrhosis?

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Dear Editor,

We read with great interest the letter by Parsikia and coworkers [1] concerning the review recently published on the management of HCV in patients with end-stage renal disease and kidney transplantation [2] and thank the authors for bringing up such a stimulating discussion, which reflects the contrasting European and American practices regarding compensated cirrhosis in the setting of kidney transplantation.

Coinciding with the comment by Parsikia and collaborators, both the KDIGO [3] and the AASLD [4] guidelines do not provide precise recommendations on the management of HCV-related cirrhosis patients with end-stage renal disease. In patients with well-compensated cirrhosis, the KDIGO recommendation of performing kidney transplant only is stated merely as a weak recommendation and within an investigational setting [3], whereas the AASLD guidelines [4] and their recent revision [5] do not explicitly provide recommendations regarding the management of patients with compensated cirrhosis and chronic kidney disease. Both guidelines, which date back to 2008 and 2009, warrant revision and updating, especially in light of the new antiviral agents which are available and can now be incorporated in the management algorithm of these patients.

In these guidelines, interferon-based antiviral therapy is considered controversial in patients who are in Stage 5D of chronic kidney disease (who are on dialysis), and it is not recommended after solid organ transplantation including kidney transplantation [4]. Although recognizing that successful antiviral therapy might improve liver disease, the KDIGO guidelines state that if the patient with well-compensated cirrhosis remains viremic, kidney transplantation alone is not recommended and the patient may become a candidate for combined kidney–liver transplantation at a later date [3]. Whereas there is evidence that the majority of patients achieving a sustained virological response show histological improvement [6] and do not relapse following the introduction of immunosuppression [7] after kidney transplant, there are limited data as to whether this has a positive impact on the progression of liver injury, and these studies have not yet taken into account the new antivirals. The latter will allow a greater window of treatment opportunities for patients with HCV awaiting kidney transplantation not only to prevent cirrhosis but also attempting to clinically improve cirrhosis, prevent future episodes of hepatic decompensation, and allow for kidney transplantation only to be performed safely. As well, after kidney transplantation, viral suppression with the new agents against hepatitis C might prove to be effective in reducing the risk of progression of liver fibrosis, hepatic decompensation, and development of cirrhosis.

At our center, combined liver/kidney transplantation has been the traditional approach only for patients on dialysis and hepatic decompensation.

In case of compensated HCV-related cirrhosis in patients on dialysis, we have not performed kidney transplantation only, to avoid the risk of hepatic decompensation that may ensue after kidney transplantation, especially during the first few months after transplant, when the strong immunosuppression might trigger HCV reactivation. Kidney transplantation only has been performed in HCV-infected individuals with liver disease, as previously reported by our group, when histological hepatic damage was moderate [8], in only two patients with Metavir score $F \geq 3$, with good long-term outcome, and no reactivation or progression of chronic hepatitis C.

In contrast, past work cited by Parsikia and collaborators [9] showed interesting data demonstrating that kidney transplant alone is feasible even in cirrhosis, provided patients are compensated, with 1- and 3-year survival rates which are comparable to those of non-cirrhotic individuals. Although a longer (5 years and beyond) observation period after kidney transplant alone is needed to evaluate what course will cirrhosis take, these results are encouraging, especially since the highest risk period of the first years after transplant was reportedly safely overcome. Thus, this should allow shorter waiting times for receiving a kidney transplant, with good outcomes both in terms of renal as well as hepatic function. It would be interesting to discuss this relatively novel approach, which challenges the belief that patients

with liver disease, especially those with advanced fibrosis or cirrhosis, may be better served with a combined liver–kidney transplantation. In our opinion, however, it is necessary to evaluate the proceedings and outcomes of other centers as well as the position of scientific societies and guidelines on this issue before adopting this strategy. Clearly, as the presence of cirrhosis increases the risk of developing hepatocellular carcinoma in HCV-positive individuals [10], and as renal insufficiency and immunosuppression may additionally increase this risk, strict monitoring after kidney transplantation is warranted. In fact, Parsikia and collaborators mention that in their experience at Einstein Medical Center (reportedly recently accepted for publication), development of neoplasms was statistically more significant in the group of patients with cirrhosis, which was attributed by the Authors to a high number of patients who had undergone previous liver or kidney transplantation.

The strategy that the future seems to hold and which marks the direction of future studies is probably the vigorous and unwavering management of liver disease with the aid of the new antivirals against HCV which allow for the use of interferon-free and ribavirin-free treatment regimens. Thus, the consideration of concomitant liver transplantation in kidney transplant candidates might be avoided, if patients achieve sustained virological response on direct acting antiviral agents, delaying or altogether avoiding decompensation, keeping in check the course of liver disease in kidney transplant recipients.

Should the Authors and other groups continue to observe positive results by performing kidney transplant only in patients with compensated cirrhosis, this practice might be extended also internationally.

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